ORIGINAL ARTICLE
LUNG CANCER

Incidental detection by computed tomography is an independent prognostic factor for survival in patients operated for nonsmall cell lung carcinoma

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ABSTRACT We studied the rate of incidental detection of lung carcinomas and its effect on long-term survival in a nationwide cohort of patients operated for nonsmall cell lung cancer (NSCLC).

All patients operated for NSCLC in Iceland during 1991–2010 were included. Demographic and clinicopathological features were compared in patients diagnosed incidentally using chest radiography or computed tomography (CT), and in those with symptomatic presentation. Multivariate analysis was used to evaluate prognostic factors.

Out of 508 patients, 174 (34%) were diagnosed incidentally; in 26% of cases by chest radiography and in 8% by CT. The CT-detected tumours were significantly smaller than symptomatic tumours, diagnosed at earlier TNM (tumour, node and metastasis) stages and more often of adenocarcinoma histology. 5-year cancer-specific survival for symptomatic *versus* incidentally diagnosed patients detected by chest radiography and CT was 41%, 57% and 68%, respectively (p=0.003). After adjusting for stage, the hazard ratio (HR) for NSCLC mortality was significantly lower for incidental diagnosis by CT (HR 0.55, 95% CI 0.31–0.98; p=0.04) compared to incidental diagnosis by chest radiography (HR 0.95, 95% CI 0.70–1.27; p=0.71) or symptomatic diagnosis (HR 1.0).

One-third of surgically treated NSCLCs were detected incidentally, with an increasing rate of incidental CT diagnosis. NSCLC patients diagnosed incidentally by CT appear to have better survival than those diagnosed incidentally by chest radiography, and particularly those who present with symptoms.

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A third of surgically treated NSCLC cases were detected incidentally; those detected by CT may have better survival http://ow.ly/S24I309M1VK

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Introduction

Lung cancer is the second most common cancer and the most frequent cause of cancer-related death in most developed countries [1]. Symptoms of lung cancer are often subtle and nonspecific, leading to delays in diagnosis [2–5]. In some patients, the disease is diagnosed incidentally, without symptoms of lung cancer, during work-up for unrelated disease. The role of incidental detection has been studied in other cancers such as renal cell carcinoma, where it has been shown to affect survival favourably [6]. Only a few studies have investigated the prognosis of patients with lung cancers detected incidentally without intention to screen [7–11]. These lung cancer patients may have different clinical characteristics and survival from those of a screening population or patients with symptoms.

Numerous screening trials have been performed using low-dose computed tomography (CT) for early detection, but the results have been conflicting [12, 13]. The National Lung Screening Trial [14] reported a 20% reduction in lung cancer mortality and a 6.7% reduction in all-cause mortality in subjects at risk who were screened using CT. This suggests that early detection by CT has a favourable effect on prognosis in the setting of a screening trial. As a result, the US Preventive Services Task Force has recommended screening for lung cancer in heavy smokers aged 55–80 years [15].

The objective of this study in a nationwide cohort was to identify the characteristics of, and to determine the survival rate for incidentally detected nonsmall cell lung carcinomas (NSCLCs) that were resected surgically, and to compare them with corresponding data for NSCLCs that were detected because of symptoms. We hypothesised that incidentally detected tumours would have a more favourable prognosis, even accounting for tumour and patient characteristics. A further goal of the study was to investigate whether increased use of thoracic imaging, especially CT, has led to an increase in incidentally detected tumours, and if so, whether there has been a change in long-term survival.

Materials and methods

This was a nationwide, population-based study of all patients who underwent pulmonary resection for NSCLC in Iceland between January 1, 1991 and December 31, 2010. Patients were identified through the Icelandic Cancer Registry, but to minimise the risk of cases being missed, two other registries were checked: 1) a central, computerised histology database at the department of pathology of Landspitali University Hospital (Reykjavik, Iceland), containing details of all lung histology specimens in Iceland and 2) the diagnosis and operation registry at Landspitali University Hospital, which is the only centre at which cardiothoracic surgery is performed in Iceland.

The study was approved by the national bioethics committee and the Icelandic Data Protection Commission. During the study period, the average population of Iceland was 283 878; ranging from 255 866 on January 1, 1991 to 318 236 on December 31, 2010.

Eight patients with small cell cancer, large cell neuroendocrine carcinoid tumour or lung metastases of nonpulmonary origin were excluded from the study. Furthermore, patients with advanced disease who underwent resection without curative intent were excluded. 12 patients were diagnosed with another primary tumour during the study period and underwent two separate operations. All tumours were staged according to the seventh TNM (tumour, node and metastasis) system of the International Association for the Study of Lung Cancer [16]. Major histological types were classified according to World Health Organization guidelines, including adenocarcinoma, squamous cell carcinoma, large cell carcinoma and adenosquamous lung carcinoma [17].

508 patients fulfilled the study requirements. Detailed clinical information, including demographics, clinical presentation and operative procedures, was gathered from the hospital records. The patients were divided into three groups: incidentally diagnosed by CT, incidentally diagnosed by chest radiography and those diagnosed after symptomatic presentation. Tumours without any symptoms attributable to lung cancer at the time of initial imaging were regarded as being incidentally diagnosed (either due to general check-up or evaluation for symptoms not attributed to NSCLC). To investigate trends in the rate of incidental detection, we divided the 20-year study period into four 5-year periods.

Patients who were considered for pulmonary resection had been reviewed by a multidisciplinary tumour board consisting of thoracic surgeons, pulmonologists, oncologists, radiologists and pathologists. The preoperative work-up varied between patients, but usually included a chest radiograph, a CT scan of the chest, upper abdomen and head, and bone scintigraphy and spirometry. Preoperative biopsies were obtained through bronchoscopy or transthoracic CT-guided needle biopsy. Mediastinoscopy was performed preoperatively in a proportion of cases, but positron emission tomography scanning was not available in Iceland during the study period.

Patients were staged postoperatively (pathological staging) using both the sixth and the seventh edition of the TNM staging system. Preoperative clinical staging was not performed uniformly and is not reported in this study.

Statistical calculations were performed using R software (version 2.11; R Foundation, Vienna, Austria). ANOVA was used to compare continuous variables between groups, and Chi-squared tests and Fisher's exact tests were used to compare categorical variables. Patients were identified as living on February 2, 2015, or their date and cause of death were noted, using data from the Icelandic Cause of Death Registry and the updated Icelandic Population Registry. Cause of death was determined from death certificates and subclassified into lung cancer related deaths and deaths from other causes. Mean follow-up was 62 months (range 1–283 months) and none of the patients were lost to follow-up. Overall and cancer-specific survival were analysed using the Kaplan–Meier method. The log-rank test was used to compare unadjusted survival curves in different groups. The Cox proportional hazards regression model was used to determine the effects of clinical and pathological parameters on NSCLC-related mortality, including the significance of incidental detection. Results from univariate analysis of parameters with a significance level of $p<0.20$ were included in the preliminary model. A subset of variables was selected for inclusion in the final model using the stepwise selection procedure. The proportional hazards assumption was validated by graphic plotting of variables and by using the global goodness-of-fit test proposed by Schoenfeld [18]. Differences with p-values <0.05 were considered statistically significant.

Results

Of the 508 patients, 174 (34%) were diagnosed with NSCLC incidentally and 334 (66%) were diagnosed due to symptoms; most commonly cough (66%), dyspnoea (38%), weight loss (29%), chest pain (29%) and/or pneumonia (28%). The incidentally detected tumours were found using chest radiography in 130 cases (75%), and 41 cases (24%) were detected using CT (26% and 8% of the whole group, respectively). The remaining three incidental tumours were detected using magnetic resonance imaging. Chest imaging in patients whose tumours were detected incidentally was undertaken for miscellaneous indications, most often at work-up for cardiovascular diseases (30%), preoperative evaluation (14%), unrelated cancer work-up (13%) or after chest trauma (10%). The incidental diagnoses were made at a tertiary referral hospital in 122 (70%) cases and at smaller health clinics in 52 (30%) cases.

The proportion of incidentally detected tumours did not differ significantly between the four 5-year periods, ranging from 33% in 1996–2000 to 36% in 2006–2010 ($p=0.89$) (figure 1). However, the proportion of tumours that were incidentally detected at CT rose steadily, from 0% in 1991–1996 to 15% in 2006–2010 ($p<0.001$). During the same period, the proportion of tumours that were incidentally detected at chest radiography declined from 33% to 21% ($p=0.01$).

Demographics and histopathological data are presented in table 1. Patients with chest radiography- and CT-detected tumours were generally older than patients with symptoms (mean 68 years for chest radiography, 68 years for CT and 65 years for symptomatic diagnosis; $p=0.04$). Compared to symptomatic diagnosis, tumours detected incidentally by CT were significantly smaller (2.6 cm *versus* 4.3 cm, $p<0.001$), were at earlier TNM stages (51% *versus* 19% stage IA, $p<0.001$), were of lower grade (28% *versus* 12%

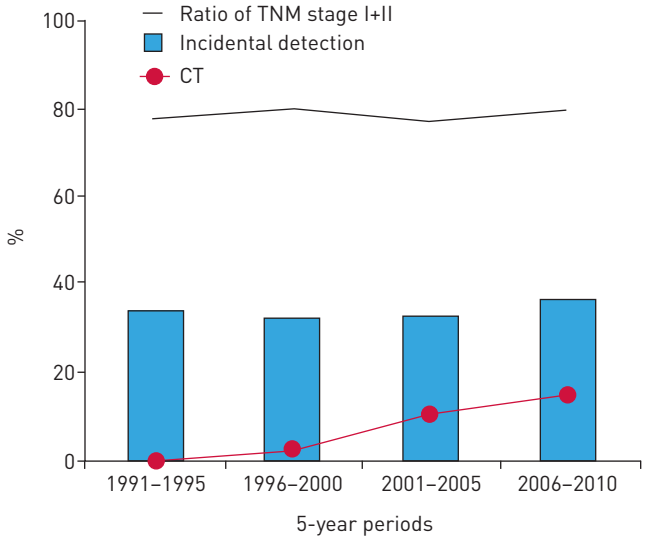


FIGURE 1 Time trends in rate of overall incidental detection of nonsmall cell lung carcinoma (NSCLC) and proportion of cases with tumour stage I+II in four separate 5-year periods from 1991 through 2010. The proportion of incidental detection by computed tomography (CT) is shown with a red line. TNM: tumour, node and metastasis.

TABLE 1 Patient demographics and histopathological data on nonsmall cell lung cancer patients diagnosed from symptoms or diagnosed incidentally by chest radiography or computed tomography (CT)

	CT	Chest radiography	Symptoms	p-value
Patients n	41	130	334	
Age years	68±11	68±9	65±10	0.04
Age >75 years	14 (34)	32 (25)	61 (18)	0.03
Male	22 (54)	60 (46)	171 (51)	0.67
History of smoking				
Ever	36 (88)	124 (95)	324 (97)	0.013
Current	22 (54)	81 (62)	230 (69)	0.07
Pack-years	38±24	43±19	41±20	0.30
COPD	10 (24)	29 (22)	96 (29)	0.37
Coronary disease	12 (29)	46 (35)	81 (24)	0.05
FEV_1 <80% predicted	9 (22)	37 (28)	126 (38)	0.04
Operation type				
Lobectomy	33 (80)	110 (85)	235 (70)	0.007
Pneumonecomy	2 (5)	3 (2)	64 (19)	<0.001
Wedge resection	6 (15)	17 (13)	35 (11)	0.60
Histology				
Adenocarcinoma	32 (78)	88 (70)	172 (52)	<0.001
Squamous cell	6 (15)	34 (27)	119 (36)	<0.001
Large cell	3 (7)	3 (2)	25 (8)	0.08
Adenosquamous	0	2 (2)	13 (4)	0.68
Tumour size cm	2.6±1.3	3.1±1.4	4.3±2.6	<0.001
Tumour stage				
IA	21 (51)	45 (35)	63 (19)	<0.001
IB	8 (20)	35 (27)	69 (21)	0.35
IIA	2 (5)	24 (19)	64 (19)	0.08
IIB	6 (15)	9 (7)	53 (16)	0.04
IIIA	4 (10)	14 (11)	65 (20)	0.04
IIIB	0	1 (1)	3 (1)	1
IV	0	2 (2)	17 (5)	0.12
Tumour grade				
Well differentiated	11 (28)	22 (18)	37 (12)	0.01
Moderate	11 (28)	53 (43)	132 (41)	0.25
Poor	16 (40)	46 (37)	133 (41)	0.68
Undifferentiated	2 (5)	2 (2)	21 (7)	0.08

Data are presented as mean±SD or n (%), unless otherwise stated. COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 s.

well-differentiated, p=0.01) and had a higher incidence of adenocarcinoma pathology (78% *versus* 52%, p<0.001). Patients with tumours detected by chest radiography showed a similar tendency, but it was less pronounced. In addition, patients with tumours detected by CT were less likely to have a history of smoking than the two other groups (88% *versus* 95% and 97% for diagnosis following chest radiography and symptomatic diagnosis, respectively), and forced expiratory volume in 1 s was less often <80% predicted (22% *versus* 28% and 38% for diagnosis following chest radiography and symptomatic diagnosis, respectively). A higher proportion of patients whose tumours were detected by chest radiography and CT had lobectomy (85% and 80%, respectively, compared to 70% for patients whose tumours were detected after symptoms; p=0.001) and a lower proportion had pneumonectomy (5% and 2% *versus* 19%, respectively; p<0.001).

Cancer-specific survival (CSS) for all patients with incidentally detected tumours (chest radiography- and CT-detected combined) was 60% at 5 years, compared to 41% for patients who presented with symptoms (p<0.001). Overall 5-year survival was 53% for all patients with incidentally detected tumours, compared to 39% for patients who were diagnosed after symptoms appeared (p=0.06).

Compared to NSCLC patients who had symptoms, 5-year CSS for patients with NSCLC detected incidentally by chest radiography and CT was 57% (p=0.01) and 68% (p=0.003), respectively (figure 2). Similarly, 5-year overall survival for such patients was 51% (p=0.3) and 59% (p=0.01), respectively (figure 3). Survival trends during the four 5-year periods for all patients are shown in figure 4.

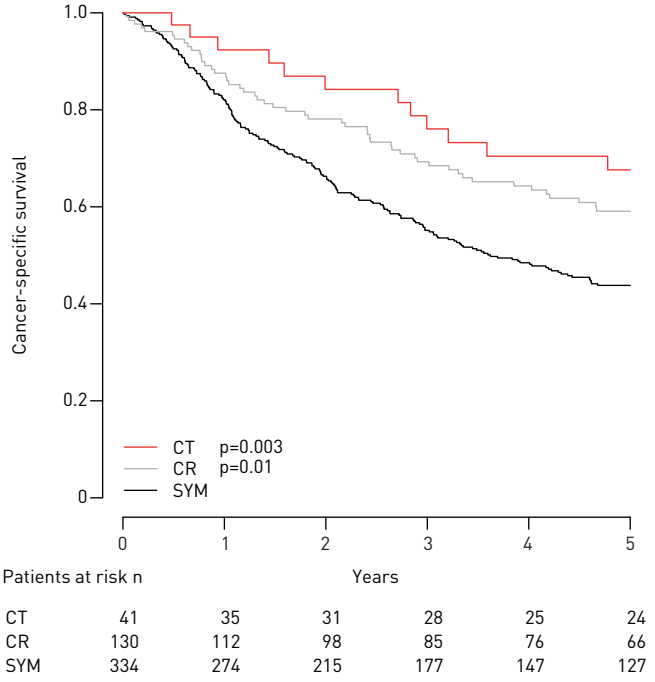


FIGURE 2 Comparison of cancer-specific survival in patients with nonsmall cell lung cancer detected incidentally by computed tomography (CT) (n=41) or chest radiography (CR) (n=130) and in patients with symptomatic presentation (SYM) (n=334).

We conducted a multivariate analysis to evaluate the effect of incidental diagnosis on NSCLC-related mortality. Due to nonproportionality, stratification was used to adjust for tumour stage. Among the significant variables (table 2) were age (hazard ratio (HR) 1.57 for patients aged ⩾75 years, 95% CI 1.22–2.04; p<0.001), undifferentiated tumour grade (HR 5.11 compared to well-differentiated, 95% CI 1.15–22.63; p=0.03) and lobectomy (HR 0.69 compared to pneumonectomy, 95% CI 0.48–0.98; p=0.04). After correction for these factors, incidental detection by CT was found to be an independent risk factor with a protective HR of 0.55 (95% CI 0.31–0.98; p=0.04) compared to patients who were diagnosed due to symptoms. However, incidental detection by chest radiography did not result in significantly reduced risk of mortality (HR 0.95, 95% CI 0.70–1.27; p=0.71).

Discussion

We studied the rate of incidental detection in a nationwide material of NSCLC in a well-defined population and the effect of incidental detection on long-term survival. Approximately one-third of the

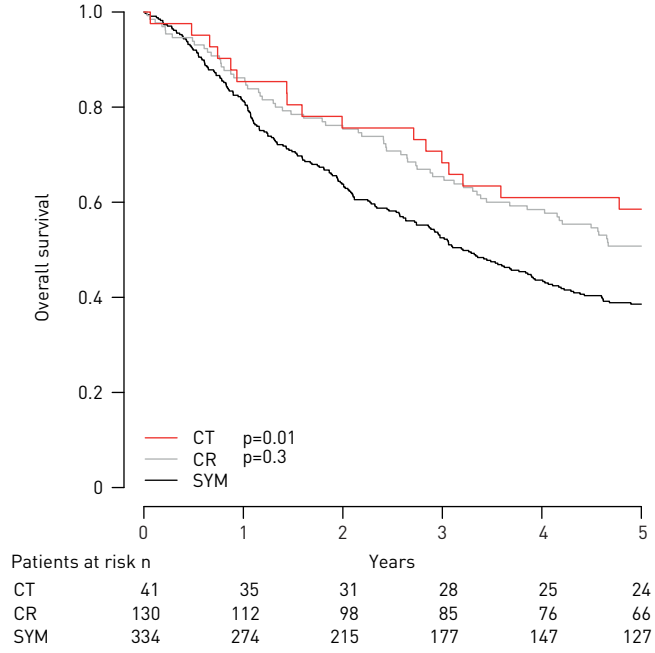
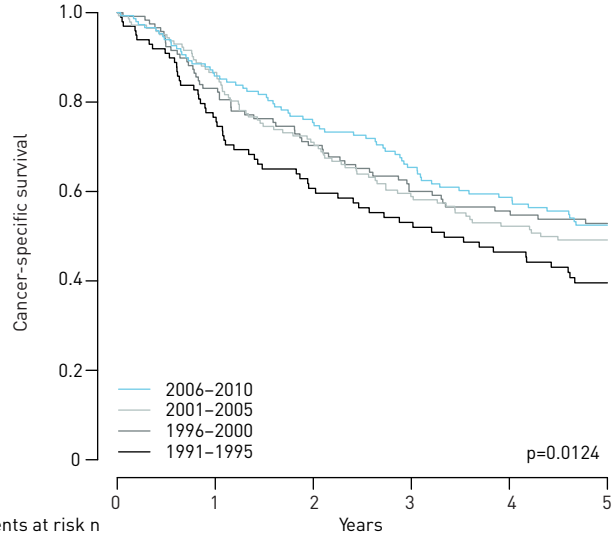


FIGURE 3 Comparison of overall survival in patients with nonsmall cell lung cancer detected incidentally by computed tomography (CT) (n=41) or chest radiography (CR) (n=130), and in patients with symptomatic presentation (SYM) (n=334).



Patients at risk n						
2006–2010	150	126	106	90	77	64
2001–2005	143	122	100	82	68	63
1996–2000	120	98	82	70	61	56
1991–1995	99	75	56	48	42	34

FIGURE 4 Unadjusted long-term cancer-specific survival in patients operated for nonsmall cell lung cancer in four 5-year periods from 1991 through 2010.

patients who underwent pulmonary resection for NSCLC from 1991 through 2010 were diagnosed incidentally. These patients had a more favourable unadjusted survival than NSCLC patients who presented with symptoms. After correcting for important risk factors for mortality, including stage at diagnosis, incidental detection by CT remained a significantly favourable prognostic factor, with a hazard ratio of 0.55 (95% CI 0.31–0.98). The hazard ratio for incidental detection by chest radiography was not statistically significant (HR 0.95, 95% CI 0.70–1.27).

TABLE 2 Cox proportional hazards model for nonsmall cell lung cancer mortality, stratified by TNM (tumour, node and metastasis) stage (n=482)

	Hazard ratio (95% CI)	p-value
Age		
<74 years	1	
⩾75 years	1.57 (1.22–2.04)	<0.001
Calendar year		
1991–2000	1	
2001–2010	0.86 (0.67–1.10)	0.23
Mode of detection		
Symptoms	1	
Chest radiography	0.95 (0.70–1.27)	0.71
CT	0.55 (0.31–0.98)	0.04
Operation type		
Pneumonectomy	1	
Lobectomy	0.69 (0.48–0.98)	0.04
Wedge resection	1.08 (0.64–1.79)	0.78
Tumour histology		
Squamous cell	1	
Adenocarcinoma	1.32 (0.99–1.77)	0.06
Large cell	0.50 (0.13–1.96)	0.32
Adenosquamous	1.56 (0.81–3.01)	0.18
Tumour grade		
Well differentiated	1	
Moderate or poorly differentiated	1.33 (0.88–2.03)	0.18
Undifferentiated	5.11 (1.15–22.63)	0.03
Tumour size (per cm increase)	0.99 (0.99–1.00)	0.38

CT: computed tomography.

Our study confirms that a large proportion of patients with NSCLC are diagnosed by incidental imaging, without any intention to screen. Furthermore, an increasing proportion of these tumours are detected by CT scanning, which seem to have similar survival and characteristics as tumours detected during screening [19].

Kawachi *et al.* [9] compared lung cancer patients detected by screening to those detected incidentally and those diagnosed from symptoms in a single-institute Japanese cohort. Their results show that compared to tumours detected from symptoms, incidentally detected tumours tended to be similar to screening-detected tumours regarding smaller size and less advanced stage.

In a single-centre study by Raz *et al.* [10], using a similar approach to the present study, the rate of incidental detection of lung cancer in 100 surgically resected patients was 36%, with no difference in stage-adjusted survival between incidentally detected and symptomatic patients. In that study, a subgroup of patients detected incidentally by CT showed a trend of lower stage-adjusted mortality with a nonsignificant hazard ratio of 0.47 (95% CI 0.14–1.49), possibly due to the small cohort size.

In a recent study from Argentina, Quadrelli *et al.* [11] found a considerably higher proportion of incidentally detected patients: 54% of the 593 patients surgically resected for NSCLC, as opposed to 34% in the present study. These differences may result from different patient demographics, medical imaging policies or awareness in the population studied. In agreement with our findings, the 5-year overall survival in that study was significantly better in the incidentally detected group: 66%, compared to 46% in symptomatic patients.

There are several possible explanations for our results. The incidentally detected tumours were more often adenocarcinomas and were generally diagnosed at an earlier stage, with smaller tumour size and lower tumour grade, all of which are known to be favourable prognostic indicators. Even though we adjusted for stage and grade, it is entirely possible that the biological behaviour of tumours differs, and that this difference is not captured by the staging and grade of the tumour. The incidence of specific subtypes of adenocarcinoma with a favourable prognosis is rising [20–24]. These subtypes may be more commonly detected without symptoms. In addition, the location of the incidentally discovered tumours could differ from those of the symptomatic ones, with more peripherally located tumours less likely to be diagnosed based on symptoms. This is in line with the fact that incidentally detected NSCLC patients more often underwent lobectomy rather than pneumonectomy, probably due to their smaller size and more peripheral location.

CSS improved significantly during the 20-year study period, whereas operative mortality (deaths within 30 days) remained similar (figure 3). It is unlikely that the increased use of CT scans would fully explain the improved survival observed during the latter half of the study, as only 8% of all NSCLC patients were diagnosed incidentally by CT. The ratio of patients diagnosed at stages I or II did not change during the study period, as would be expected with increased CT-based detection of NSCLC (figure 1). Factors such as improved surgical technique, adjuvant chemotherapy and radiotherapy and more accurate staging of the tumours could contribute to more favourable survival.

It could be argued that the more favourable survival in our study may have been due to lead-time or overdiagnosis bias, where apparently increased survival time would result from earlier diagnosis of tumours with no postponement of death [25]. However, these types of bias may be more relevant when assessing the efficacy of early detection programmes, where long-term mortality is the gold standard. In the present study, the overall long-term survival of asymptomatic patients with NSCLC detected by CT was 20% higher than in symptomatic patients at 5 years (59% *versus* 39%, p=0.02). These results are in line with the National Lung Screening Trial, which indicates that CT-based screening has a real impact on prognosis. This survival benefit was completely absent from previous screening trials using chest radiography [14, 25, 26].

A notable strength of this study is that our cohort consisted of patients from an entire population, all of whom were operated at a single centre with 100% follow-up. The results were therefore less likely to have been affected by tertiary referral. One possible limitation of the study is that it was retrospective, where the classification of incidental detection relied on findings in medical records. Thus, lung-cancer related symptoms may have been underreported, and therefore the ratio of incidental detection may have been overestimated. In this study we only include surgically resected patients, which may be regarded as a limitation. However, we believe that our cohort is well defined and important, reflecting those patients with potentially curable disease.

In conclusion, one-third of the surgically treated NSCLC patients were detected incidentally, with an increasing proportion being detected by CT. To our knowledge, the present study is the first and only nationwide population-based study in the literature to have analysed the incidence and survival of incidentally detected lung cancer patients. Patients who were diagnosed incidentally by CT generally had smaller tumours, were at a less advanced stage of the disease and had a more favourable survival rate than patients whose NSCLC was detected incidentally by chest radiography or who presented with symptoms.

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